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EXAMINER	
KATCHEVES, KONSTANTINA T	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,980	OW ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 32-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 32-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/24/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 and 32-47 are pending in the present application.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/620800, filed 29 July 2000. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference

required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 and 32-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,746,870 ("'870"). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '870 would necessarily anticipate the claims of the present application.

The invention of the instant claims is broadly drawn to a eukaryotic cell comprising a single structural element, *i.e.* a prokaryotic recombinase wherein the recombinase can mediate site-specific recombination between two recombination sites but in the absence of an additional factor that is not present in the eukaryotic does not mediate recombination between two hybrid recombination sites. The invention of the

instant claim is also drawn to a nucleic acid comprising a polynucleotide sequence comprising a recombinase operably linked to a promoter. The invention of the instant claims is also broadly drawn to a eukaryotic cells comprising a recombinase selected from the group consisting of ΦC31 integrase, coliphage P4 recombinase, a Listeria phage recombinase, a bacteriophage R4 Sre recombinase, a CisA recombinase, an XisF recombinase, or a Tn4451 TnpX recombinase. The claims are also drawn to eukaryotic cells comprising a polynucleotide that encodes ΦC31 recombination sites, attB and attP, wherein the polynucleotide further comprises a gene of interest and selectable marker. The cells further comprise a ΦC31 integrase polypeptide.

The invention of '870 is drawn to a method of making a eukaryotic cell having the above elements. For example the eukaryotic cell made by the method of '870 comprise nucleic acids encoding attB and attP sites, also comprising nucleic acids encoding recombinases operable linked to a repressible promoter. Additionally, the eukaryotic cell made by the method of '870 also comprises a recombinase selected from the group consisting of ΦC31 integrase, coliphage P4 recombinase, a Listeria phage recombinase, a bacteriophage R4 Sre recombinase, a CisA recombinase, an XisF recombinase, or a Tn4451 TnpX recombinase. Therefore, the eukaryotic cell of the claims of the instant application would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made in view of the patented claims of '870.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12 and 36-47 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term eukaryotic cell of the claims as contemplated in the specification includes the cell is present or is intended to be present in a human being such that said cell would be integrated into the human being and therefore an inseparable part of the human itself. In particular, the specification at page 22, lines 3-6, states that the methods of using the cell are useful for producing transgenic and chimeric animals of most vertebrate species. Such species include, but are not limited to, nonhuman mammals, including rodents such as mice and rats, rabbits, bovines such as sheep and goats, porcines such as pigs, and bovines such as cattle and buffalo. [emphasis added]". The phrase "included, but are not limited to, non-human animal" necessarily renders the claims to include human animals. Therefore, the scope of the claim encompasses a human being, which is non-statutory subject matter. As such the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The nature of the invention is a transgenic or chimeric animal which comprises a eukaryotic cell comprising a prokaryotic recombinase polypeptide or a nucleic acid that

encodes a prokaryotic recombinase, wherein the recombinase can mediate site specific recombination between a first recombination site and a second recombination site.

The breadth of claims is very broad. In the instant case, the breadth of the claims encompasses a transgenic or chimeric animal, *e.g.* claim 12. Moreover, the specification contemplates such animals on page 22, for example. Thus, the claims encompass any transgenic or chimeric animal containing the eukaryotic cell of the claims.

The amount of guidance and working example in the specification is limited. The specification does not provide an enabling disclosure to make said transgenic animal. Page 21 also clearly states that: "[t]he methods of the invention are particularly useful for obtaining transgenic and chimeric multicellular organisms that have a stably integrated exogenous polynucleotide or other stable rearrangement of cellular nucleic acids." The specification contemplates contacting fertilized oocytes with a vector that includes the polynucleotide of interest flanked by recombination sites to generate a transgenic or chimeric animal having specific modifications in its genome.

The specific examples in the specification fail to teach the transgenic animals embraced by the breadth of the claims. The specific examples teach for example the organism *S. pombe* in Example 1, the CHO host cells in Example 2 and plant cells in Example 4, for example. The specification also fails to teach how to use a transgenic animal with said genotype but without a particular phenotype for the disclosed utility. The phenotype of the knockout animal is the essential element that is required to practice the use of the invention. Without teaching from the specification, one skilled in

the art would have to turn to prior art for guidance to make and use the transgenic animal as claimed.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). Thus, the phenotype of a heterozygous transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic animals that exhibit no phenotype or that exhibit transgene dependent phenotypes.

In addition, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph 1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). The particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with any phenotype as broadly claimed is unpredictable.

Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell must be available to carry

out the method. To date, there is no teaching from the art that homologous recombination in a somatic cell and subsequent introduction of said cell to a blastocyst would generate an offspring carrying said gene mutation. The specification does not teach such a method either. The only species in which the ES is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (Mullins et al. p.1558, column 2, paragraph 1). Therefore, no transgenic animals can be made for any species other than the mouse at the time of filing.

In view of the limited guidance in the specification and the unpredictability of the art, one skilled in the art would have to engage in undue amount of experimentation overcome the problems as discussed above. Therefore, the invention is not enabled as claimed.

Claims 9 and 35 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the following reasons.

Where the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner, access to the biological material may be necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. Courts have recognized the necessity and desirability of permitting an applicant for a patent to supplement the written disclosure in an application with a deposit of biological material which is essential to meet some requirement of the statute with respect to the claimed invention. Merck and Co., Inc. v. Chase Chemical Co., 273 F. Supp. 68, 155 USPQ 139 (D. N.J. 1967); In re Argoudelis, 434 F.2d 666, 168 USPQ 99 (CCPA 1970).

Applicant claims the plasmid construct, pLT43, in the instant claims. In order to sufficiently enable the claimed plasmids, Applicant must make a biological deposit of any claimed plasmid. The deposit rules (37 CFR 1.801 - 1.809) set forth examining procedures and conditions of deposit which must be satisfied when a deposit is required. See MPEP 2402-2404.

Claim1-12 and 32-47 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is established by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the

invention. . .[emphasis added]." A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The instant claims are drawn to eukaryotic cell reciting a "additional factor" and "two hybrid recombinase recombination sites" wherein the in the absenxe of said additional factor recombination between the "two hybrid recombinase recombination sites" is not mediated. The "additional factor" and the "two hybrid recombinase recombination sites" are each broad genuses which encompass are larged number of species for which Applicant has neither disclosed a representative number of species nor disclosed a structure function relationship such that one of skill in the art would reasonably conclude that Applicant was in possession of the genuses claimed.
The specification's disclosure is limited to disclosures of attL and attR as the hybrid recombinations sites but fails to disclose what the additional factors may be or even the structural characteristics of those additional factors.

Therefore, Applicant has failed to satisfy the written description requirement in two ways. First, as to the hybrid recombinase recombination sites, Applicant has merely disclosed one species, attL and attR, which absent some disclosure of a common

structural feature that are shared by all hybrid recombinase recombination sites are not a sufficient number of representative species of the genus. Second, as to the additional factor, Applicant has not disclosed any representative species of additional factors and has not disclosed identifying structural characteristics of the genus additional factors to adequately describe the genus. Absent such teachings and guidance, the specification does not describe the claimed genuses in such full, clear, concise and exact terms so as to indicate that Applicant had possession of the claimed genuses at the time of filing of the present application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36, 37, 42, 43, 44, 45, 46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 claims a "first bacteriophage ΦC31 recombination site [emphasis added]." The claim, however, fails to refer to any other or second recombination site, which renders the metes and bounds of the claims unclear. Moreover, the claims that depend from claim 36 are subject to this rejection for the foregoing reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 4-8, 10-12 and 32-34 rejected under 35 U.S.C. 102(e) as being anticipated by Crouzet et al. (US Patent Number 6,143,530) (hereinafter "Crouzet").

The invention of the instant claims is broadly drawn to a eukaryotic cell comprising a single structural element, *i.e.* a prokaryotic recombinase wherein the recombinase can mediate site-specific recombination between two recombination sites but in the absence of an additional factor that is not present in the eukaryotic does not mediate recombination between two hybrid recombination sites. The invention of the instant claim is also drawn to a nucleic acid comprising a polynucleotide sequence comprising a recombinase operably linked to a promoter.

Crouzet discloses a eukaryotic cell comprising a prokaryotic recombinase or a construct introduced into the cell. The recombinase may be controlled by inducible or constitutive promoters. See column 7, lines 45-67. Crouzet also discloses that the

recombinase may be encoded on the same plasmid as the recombinase recognition sequences attB and attP, which further comprises a marker gene. See Column 5, lines 30-40, described the plasmid comprising attB and attP and column 7, lines 57-61. The eukaryotic cells of Crouzet comprise the elements of the present claims and the recombinase found in the cells claimed by the instant application functions to mediate recombination between the attB and attP sequences the invention of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 32-34 and 36-47 rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet as applied to claims 1, 2, 4-8, 10-12 and 32-34 above, and further in view of Thorpe et al. (PNAS Vol.95 1998) (hereinafter "Thorpe").

The invention of the instant claims is broadly drawn to a eukaryotic cells comprising a recombinase selected from the group consisting of ΦC31 integrase, coliphage P4 recombinase, a Listeria phage recombinase, a bacteriophage R4 Sre recombinase, a CisA recombinase, an XisF recombinase, or a Tn4451 TnpX recombinase.

The claims are also drawn to eukaryotic cells comprising a polynucleotide that encodes ΦC31 recombination sites, attB and attP, wherein the polynucleotide further comprises a gene of interest and selectable marker. The cells further comprise a ΦC31 integrase polypeptide.

Crouzet is relied upon as described above. Crouzet fails to teach that the recombinase of the claims is ΦC31 integrase.

Thorpe discloses a eukaryotic cell comprising attP and attB recombination sites that is contacted with ΦC31 integrase. The integrase is shown to catalyze recombination of the attB and attP sites. The integrase is expressed from the *tac*

promoter on pHS33. Thorpe, further discloses that ΦC31 integrase only catalyzes recombination between attP and attB and not the products of that recombination, attL and attR sites. See page 5505, column 2; page 5506, column 2; page 5508, column 1; and figure 3(b).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a cell comprising ΦC31 integrase. One of ordinary skill in the art would have been motivated to use the ΦC31 integrase because according to Thorpe teaches that the ΦC31 integrase is shown to catalyze recombination of the attB and attP sites. Thorpe explicitly teaches that ΦC31 integrase does not facilitate recombination of attL and attR sites which are formed as products of the recombination of attB and attP sites. Similarly, Crouzet teaches eukaryotic cells comprising attB and attP sites for recombination and recombinases and integrases that recognize the attB and attP sites. Since Thorpe explicitly teaches an integrase that recognizes attB and attP sites, which are evident in the cells of Crouzet, one of ordinary skill in the art would be motivated to produce eukaryotic cells comprising ΦC31 integrase. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is

(571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636